Beryllium Toxicity In Relation To Chemical Forms and Particle Sizes

[1] Muller C, [2]Salehi F, [2]Mazer B, [3]Truchon G, [4]Chevalier G, [1]Philippe S, [3]Cloutier Y, and [1]Zayed J.

1University of Montreal, Department of occupational and environmental health

2 McGill, University, Meakins Christie Laboratories

3Institut de recherche en santé et sécurité au travail (IRSST)

4University of Quebec in Montreal

Threshold limit value (TLV) for Be

- **Quebec TWA-TLV : 2007 → 0,15 µg/m^3**
- **Before 2007 → 2,0 µg/m^3**
- **NIC→ 0,05 µg/m^3 (ACGIH, 2008)**

Immunological reactions observed in affected individuals (BeS;CBD)

- Be-specific hypersensitivity responses involving CD4+ T-lymphocytes.
- Production of T helper 1 (Th1) type cytokines.
- Inflammation in the lung.

Amicosante at al.,2006, Fontenot et al.,2002

Risk factors

- Air Be concentration
- Particle size
- Chemical form
- Duration of exposure
- Genetic susceptibility of individuals

Henneberger et al.,2001; Kent et al.,2001, Maier et al., 2003

Objective

Assessment of the toxicity of Be following inhalation – nose only - exposure according to particle size and chemical species

Be species and particle sizes

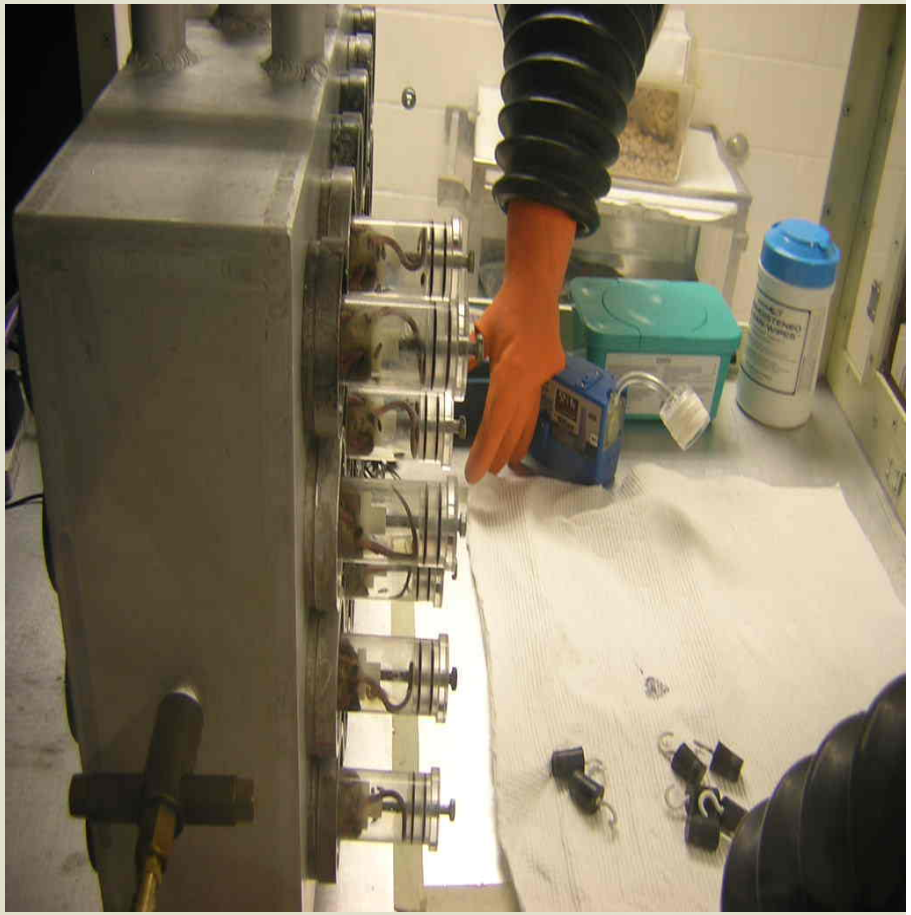
Three chemical forms

- Be
- BeO
- AlBe

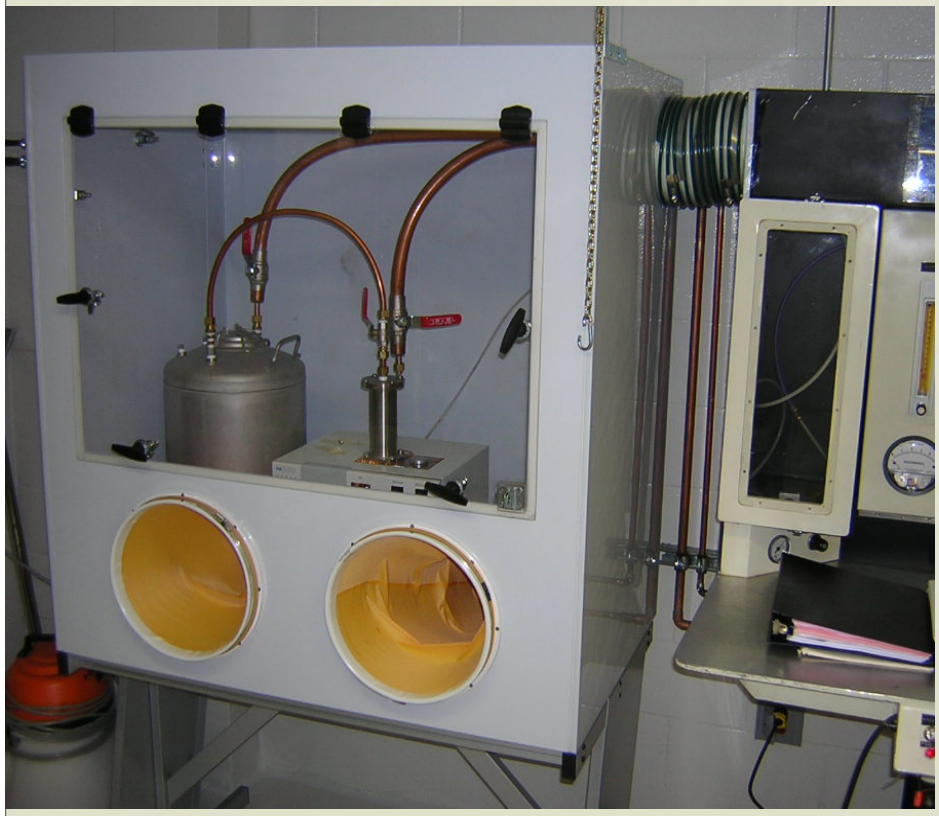
Two particle sizes

- Fine (F)
- Total (T)

Acclimatization



Intox Chamber



Methods

- **Exposure duration : 6h/d, 5 d/w, 3 w**

- **245 mice, 7 Groups (n=35)**
  - **1: control group**
  - **2: Be-T**
  - **3: Be-F**
  - **4: BeO-T**
  - **5: BeO-F**
  - **6: BeAl-T**
  - **7: BeAl-F**

Methods

Level of exposure → 250 µg/m^3

- **One week after exposure, mice were sacrificed (28 d)**
- **5 mice/group were sacrificed 3 weeks after the end of exposure (42 d)**

Monitoring

Evaluation of a methodology for Controlling Beryllium Exposure in laboratory setting

Results show that the protective measures applied during this research have been effective.

Tissue sampling

- Urine (1/week)
- Lung
- Spleen
- Liver
- Kidney
- Blood

Analysis

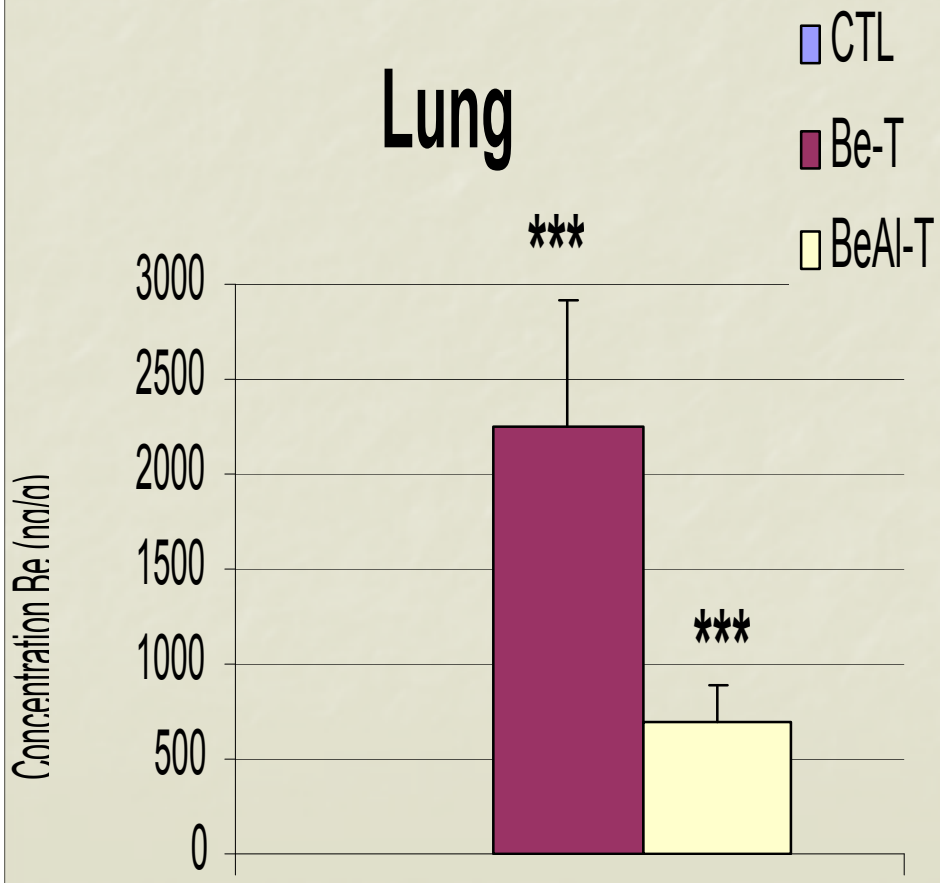
- Tissue concentration (ICP-MS)
- Lung histology
- Cytokine measurement (ELISA)
- Flow Cytometry
- BeLPT

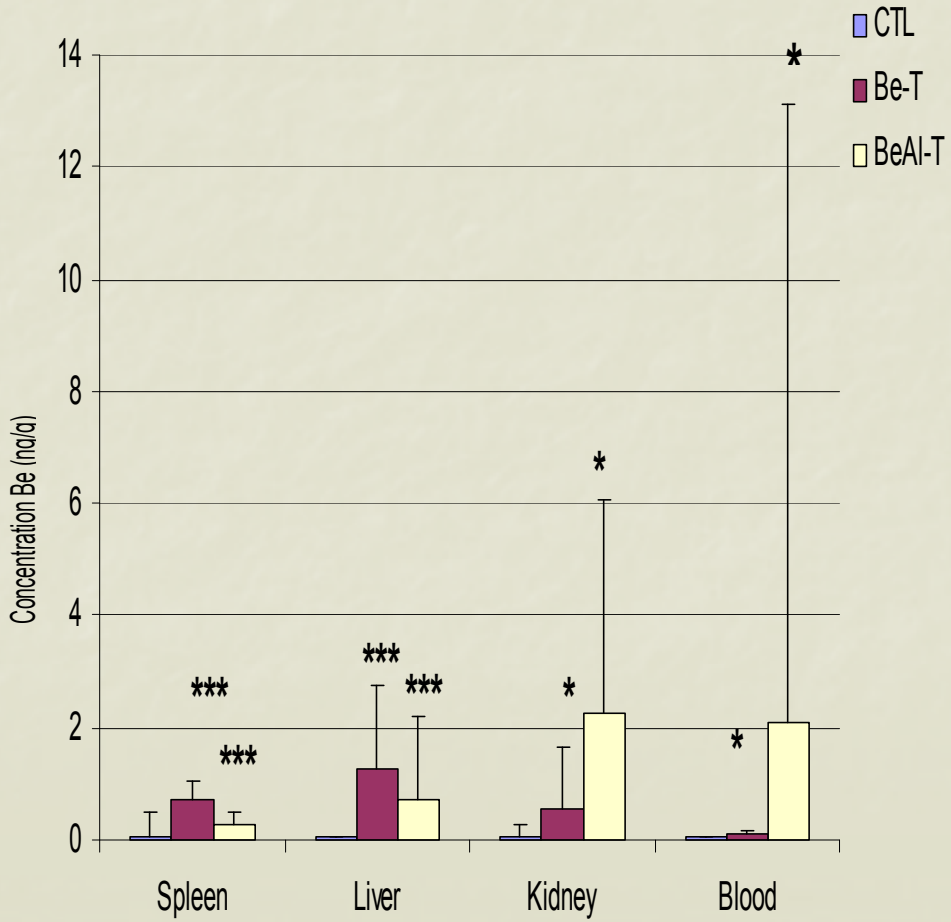
RESULTS

Be particle size in the inhalation chamber

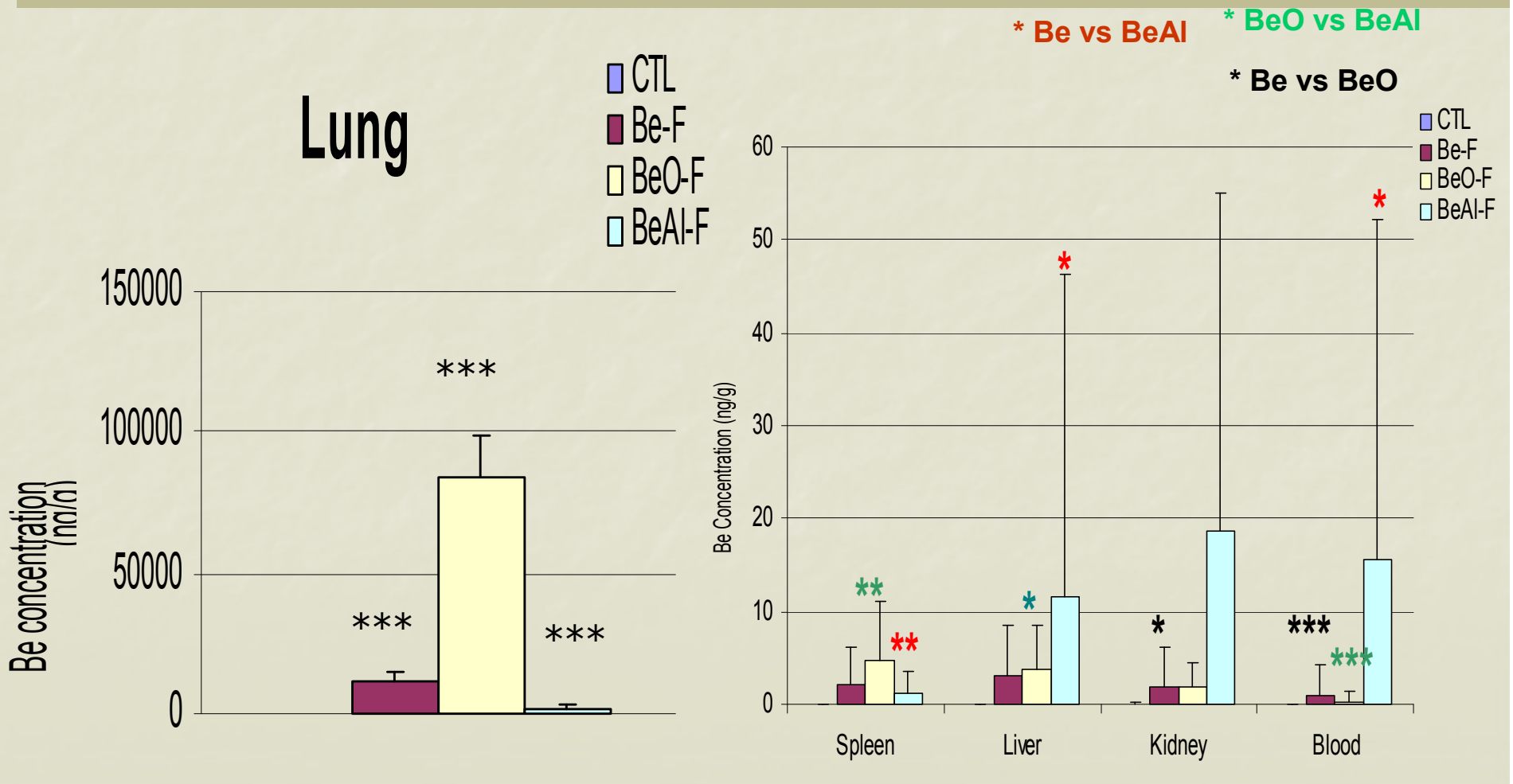
Chemical form	MMAD (µm ± GSD)
Be-T	4.1 ± 0.71
Be-F	1.5 ± 0.12
BeO-T	0.41 ± 0.14
BeO-F	0.41 ± 0.03
BeAl-T	6.5 ± 1.96
BeAl-F	4.4 ± 1.64

Tissue concentrations Be-T vs BeAl-T

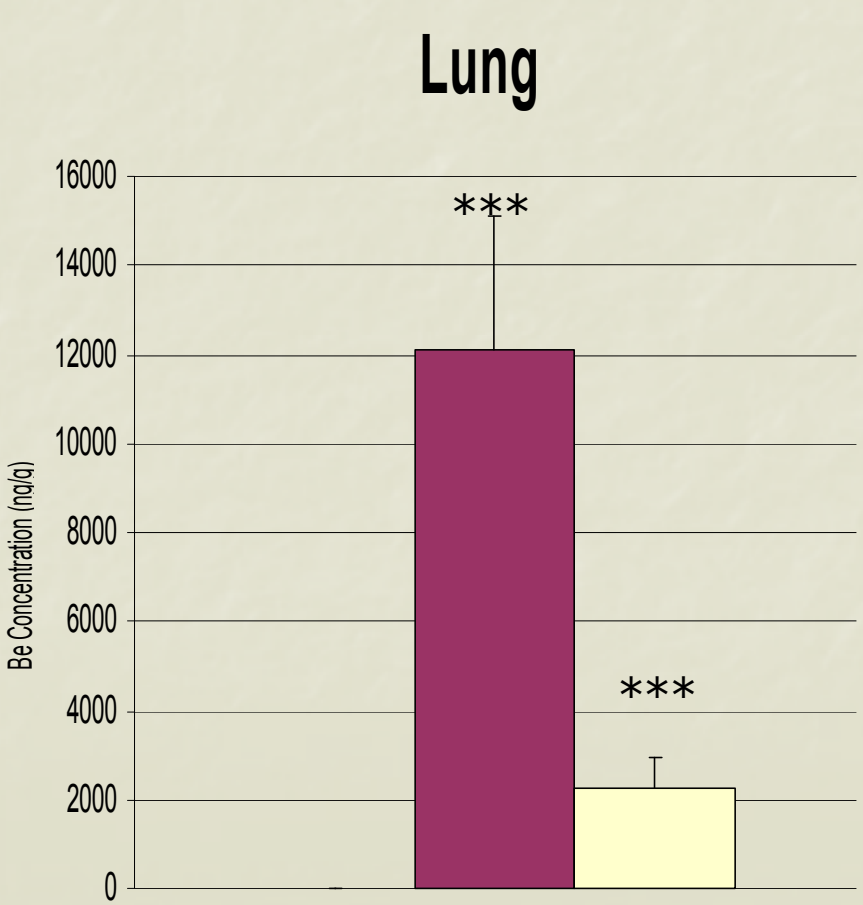


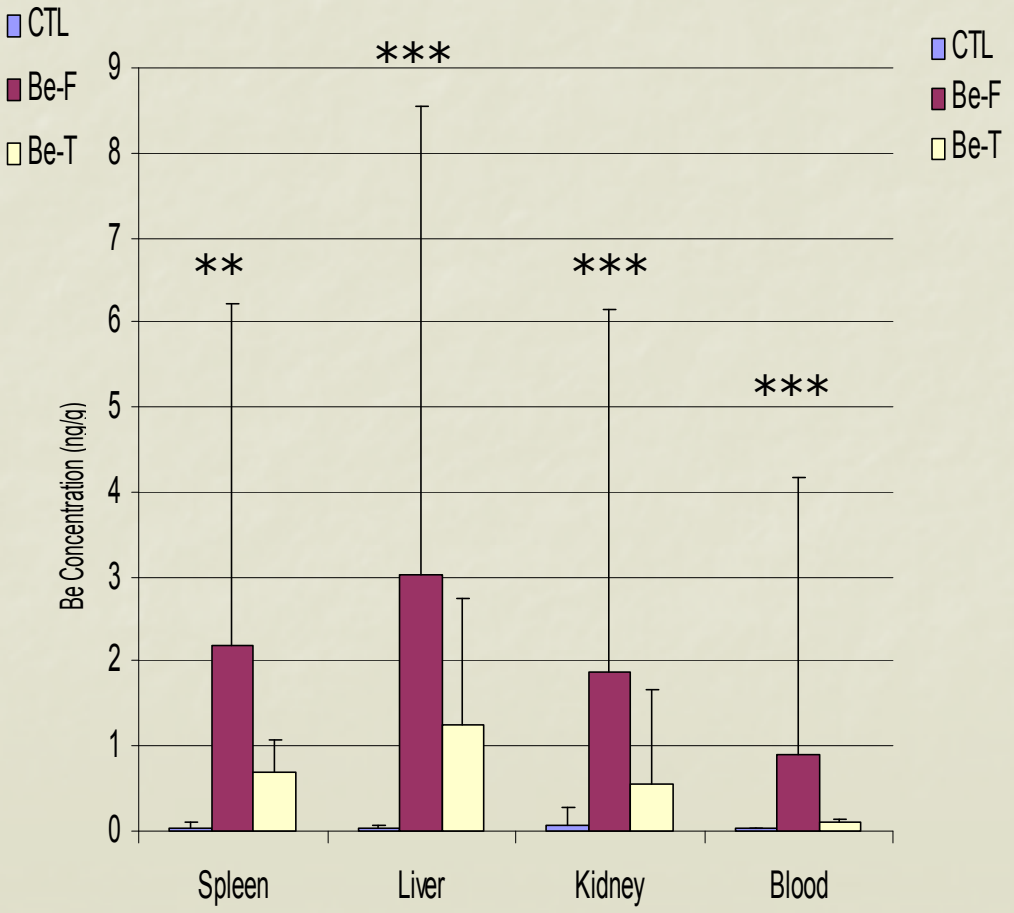


Tissue concentrations
Be-F vs BeO-F vs BeAl-F

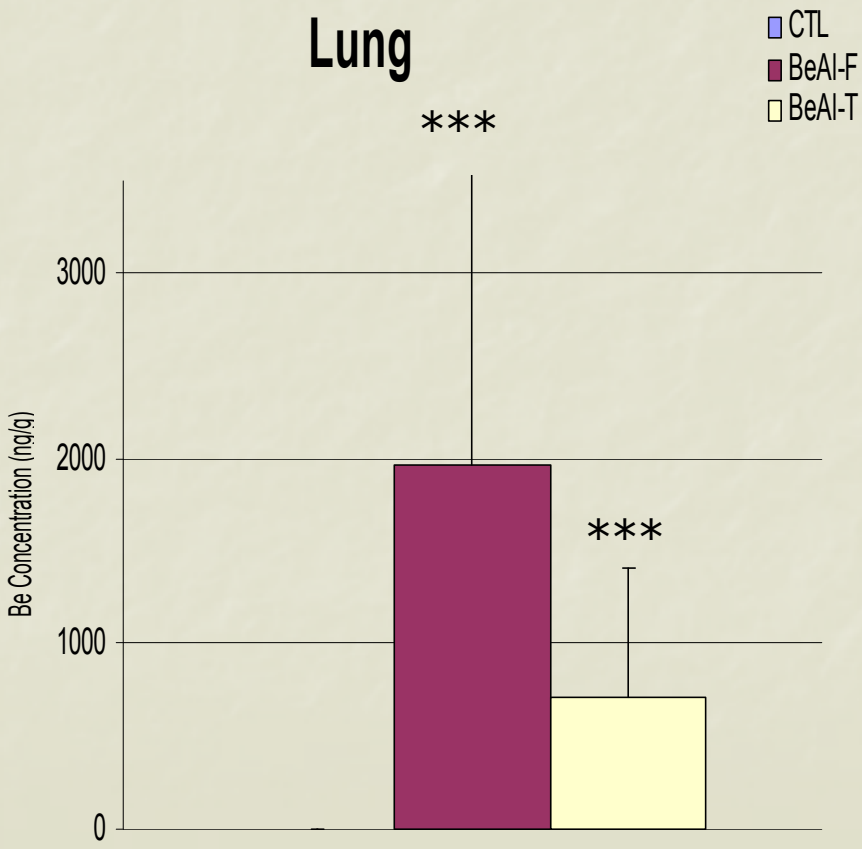


Tissue concentrations Be-F vs Be-T

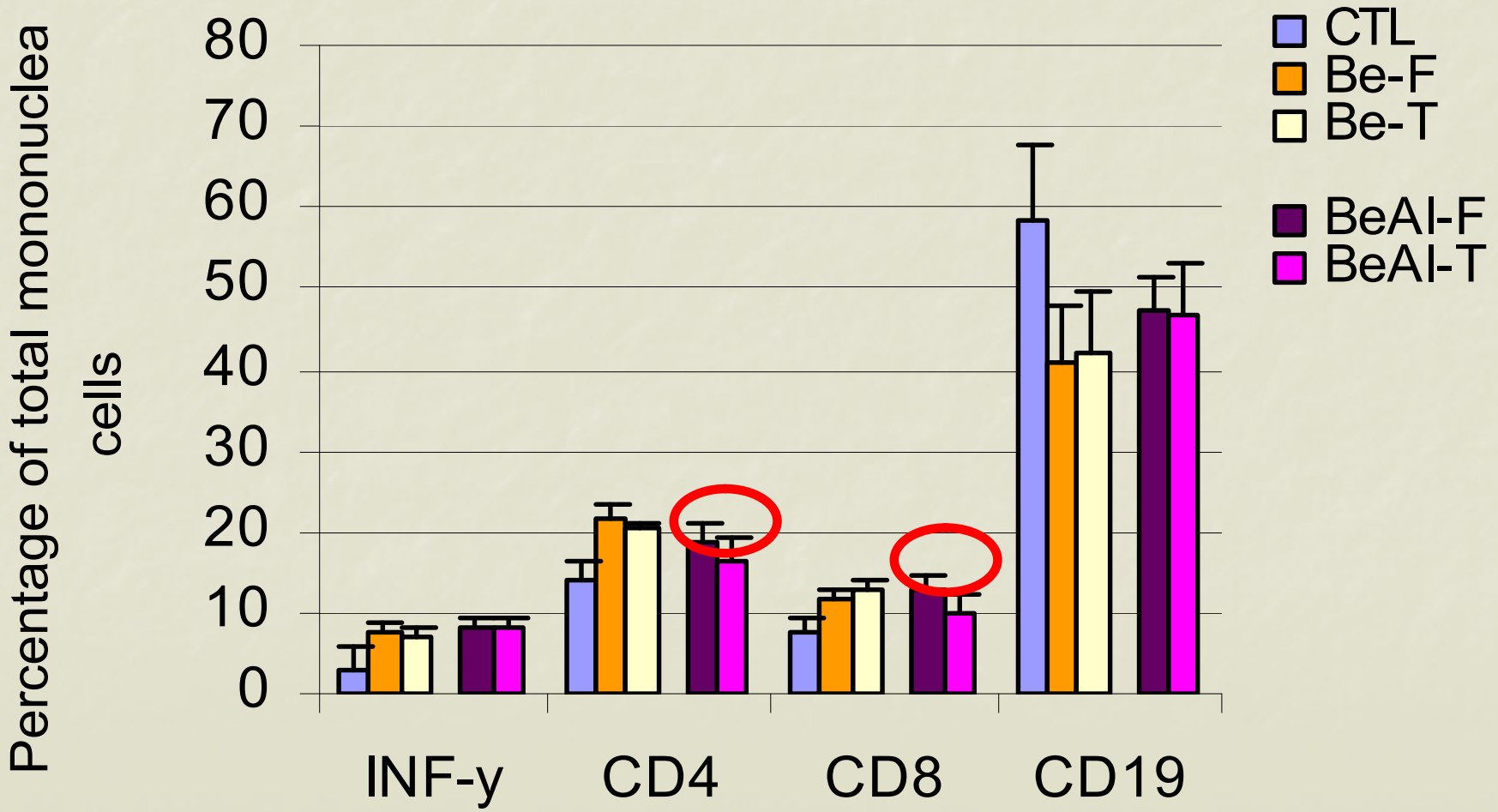




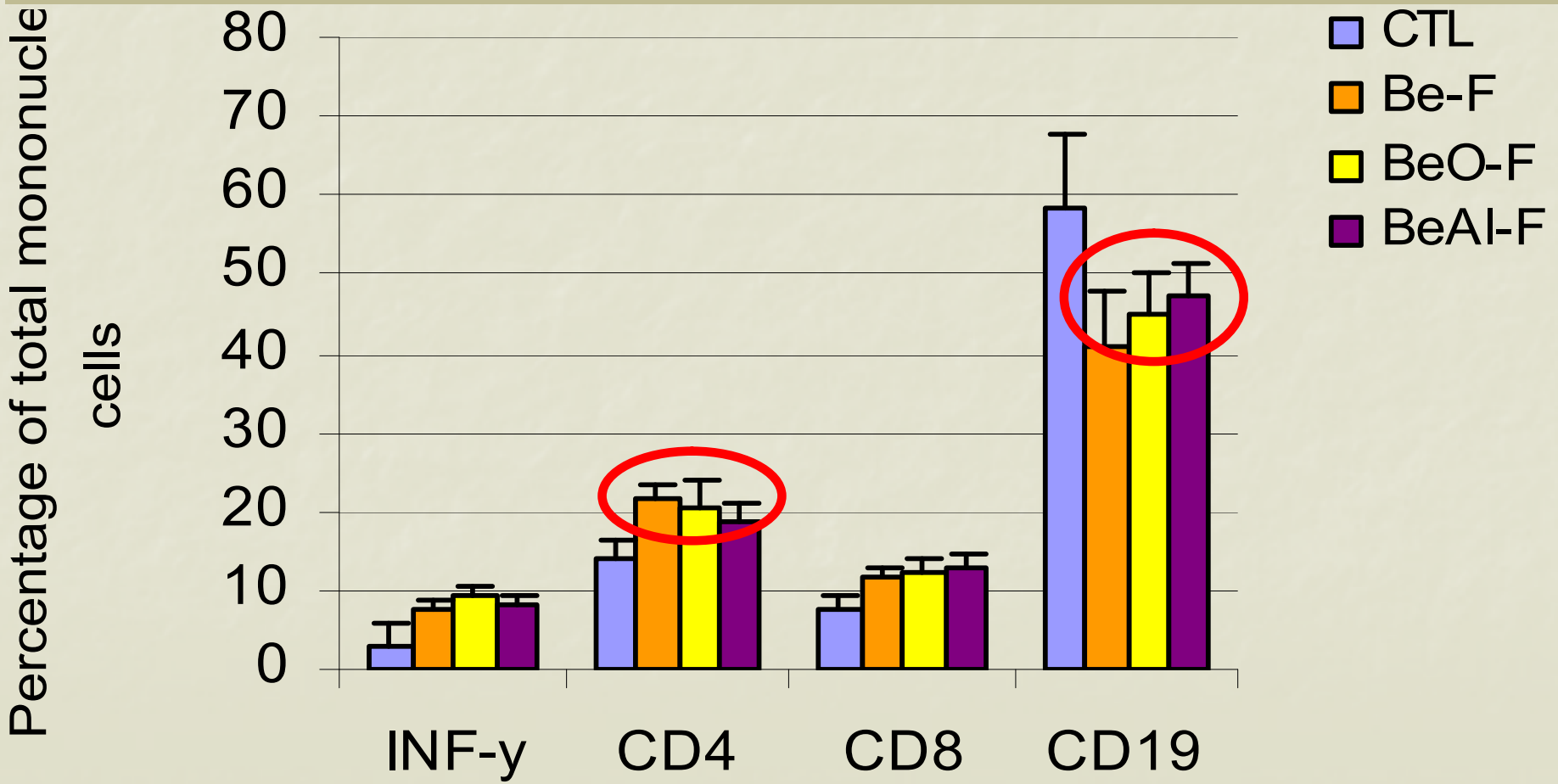
Tissue concentrations BeAl-F vs BeAl-T



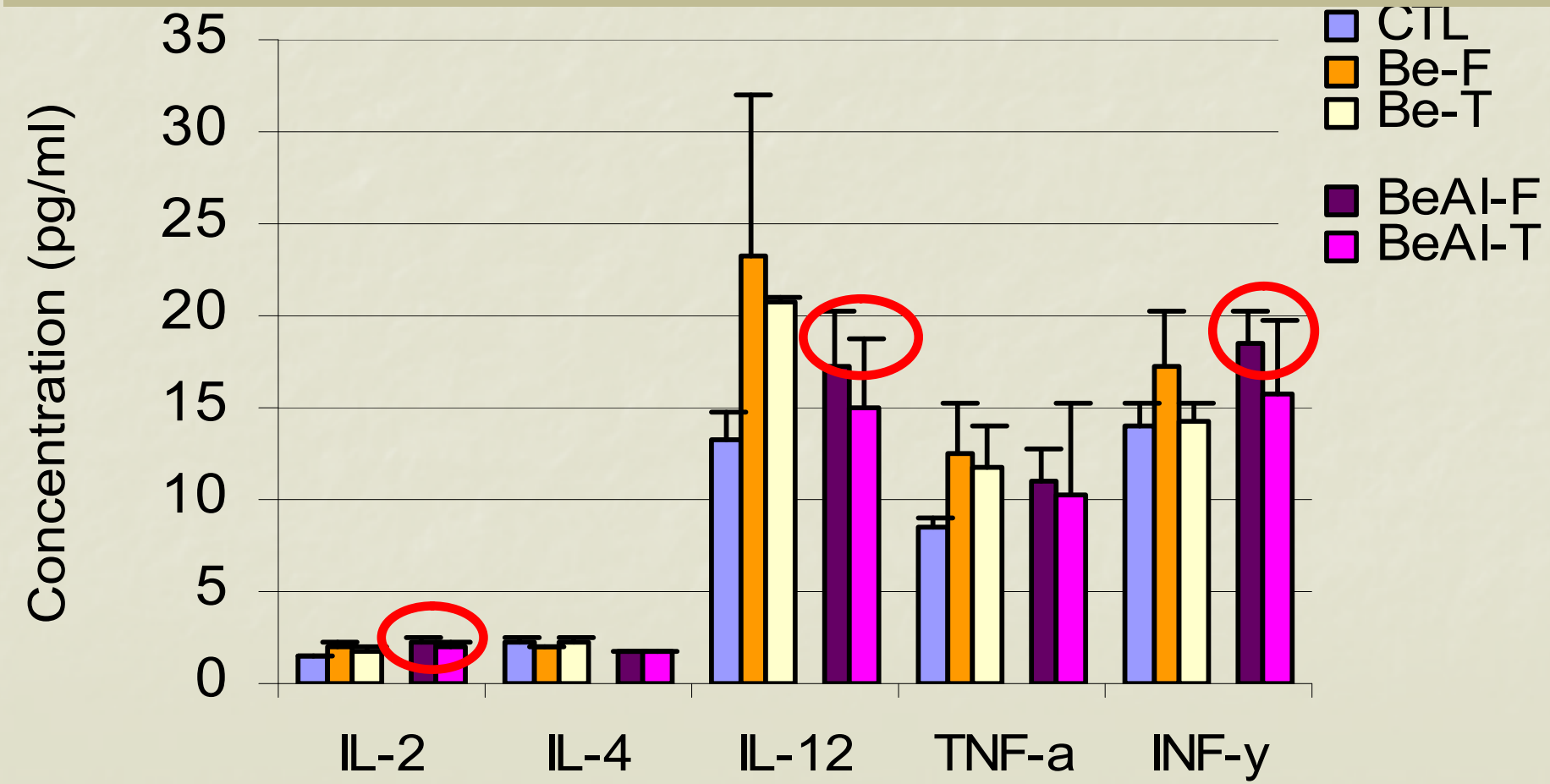
Flow Cytometry
F vs T



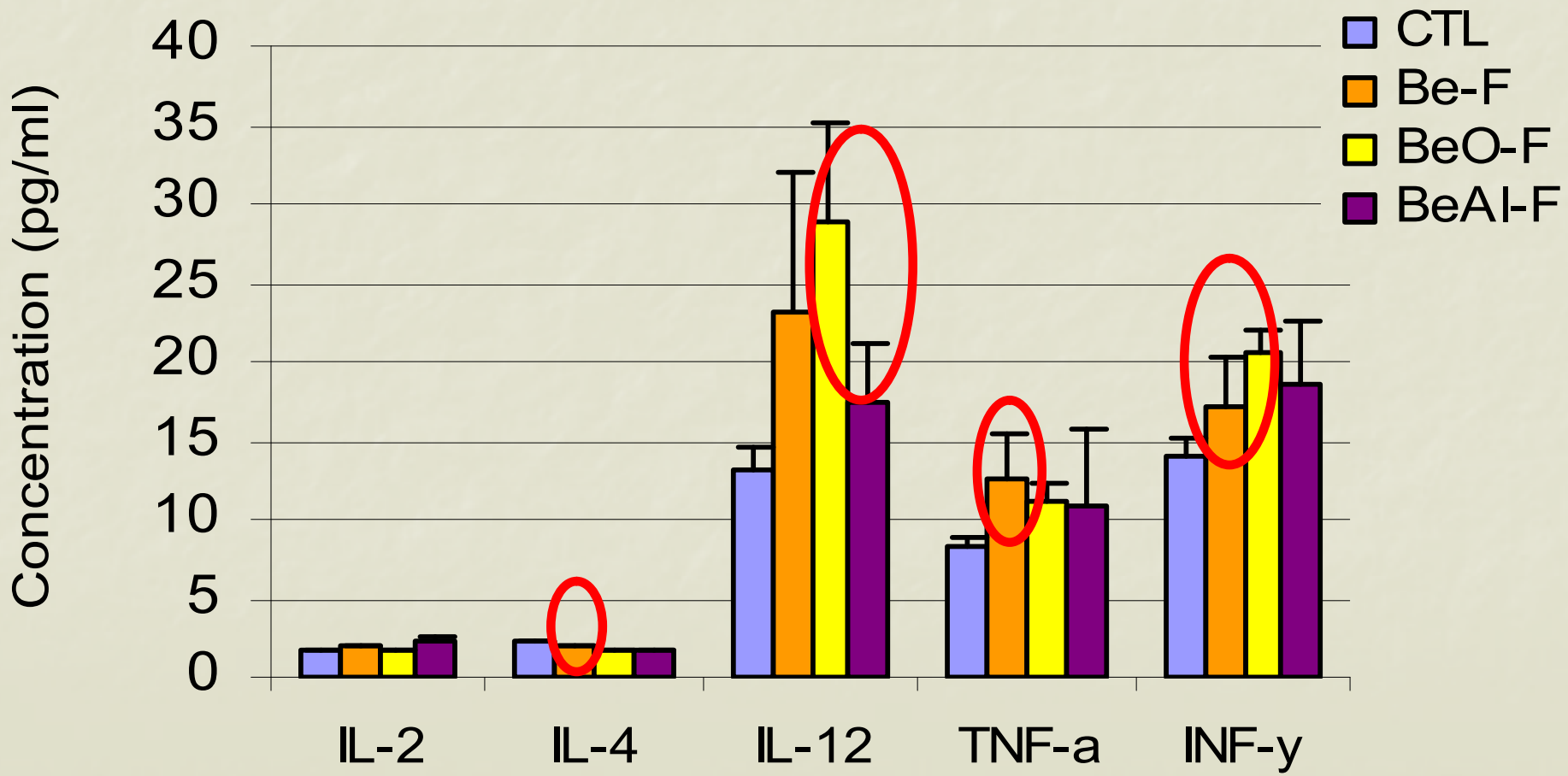
Flow Cytometry
Be-F vs BeO-F vs BeAl-F



Cytokine concentrations F vs T

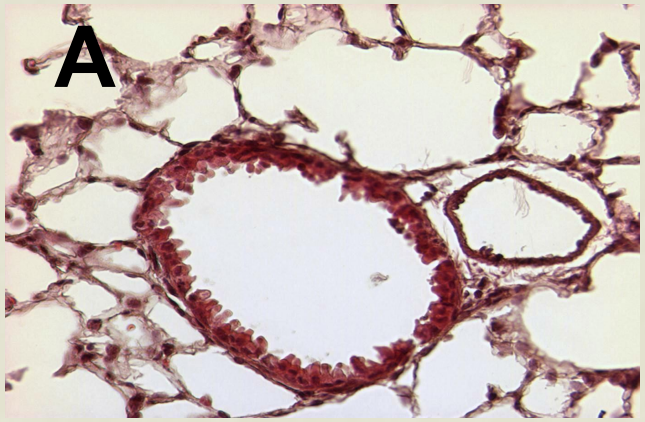


Cytokine concentrations Be-F vs BeO-F vs BeAl-F

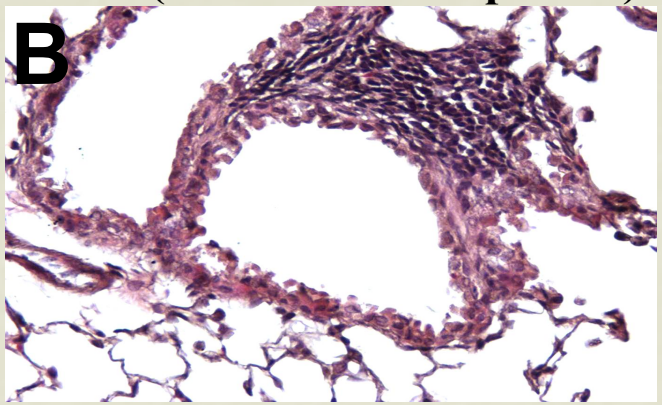


Histology of lung
Mice exposed to Be

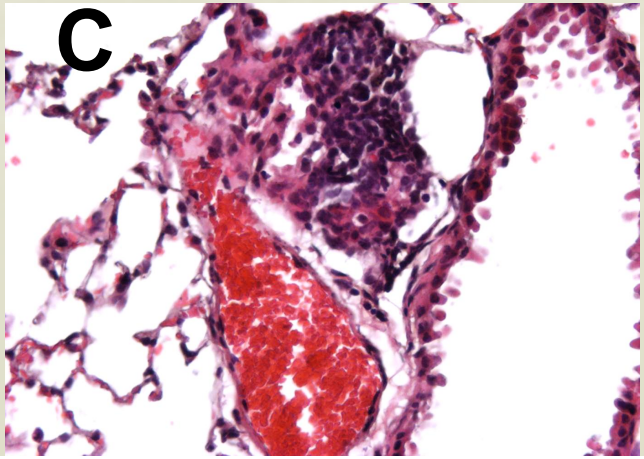
Control group



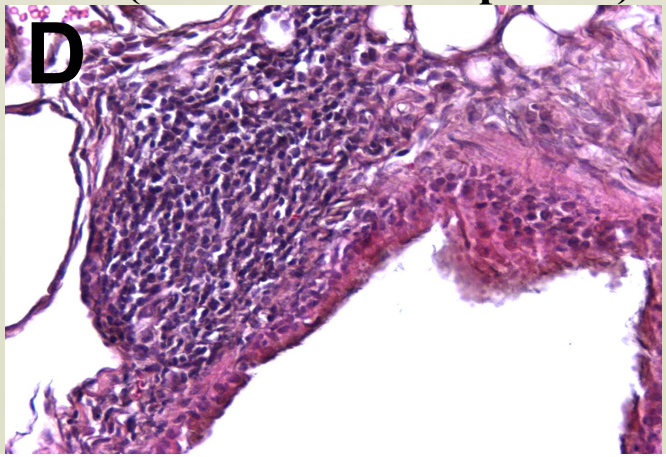
Be-F (1 week after exposure)



Be-T (1 week after exposure)

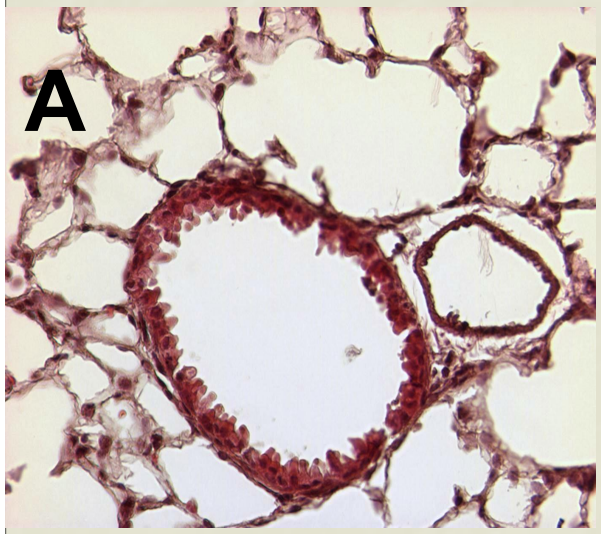


Be-F (3 weeks after exposure)

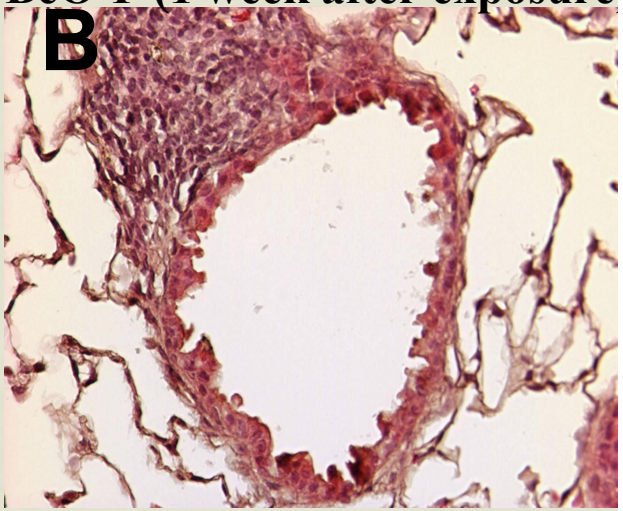


Histology of lung
Mice exposed to BeO

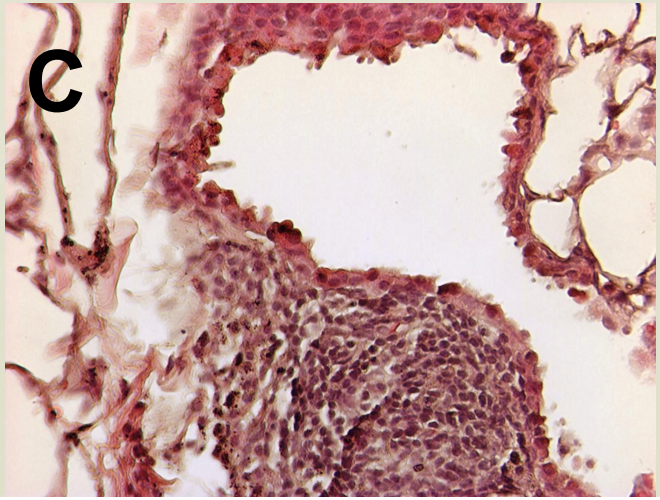
Control group



BeO-F (1 week after exposure)

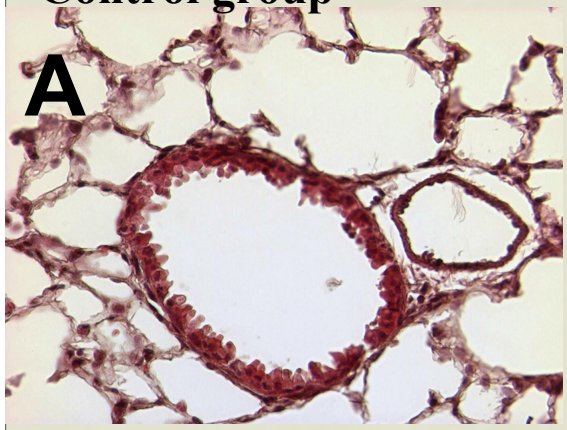


BeO-F (3 weeks after exposure)

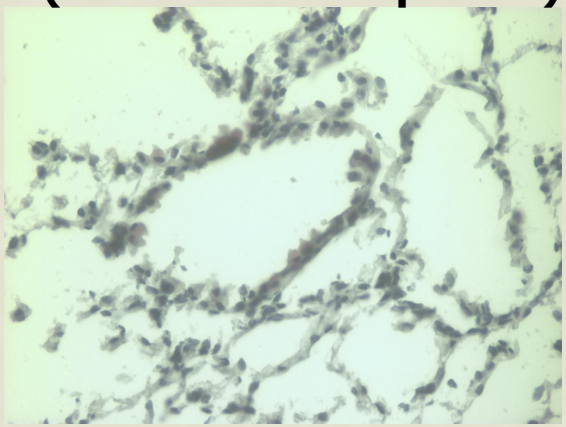


Histology of lung in mice exposed to BeAl

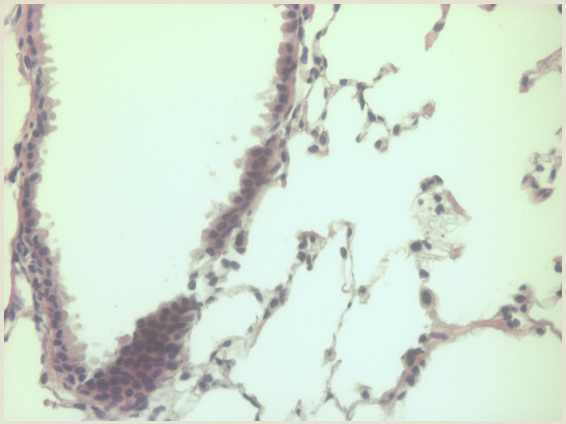
Control group



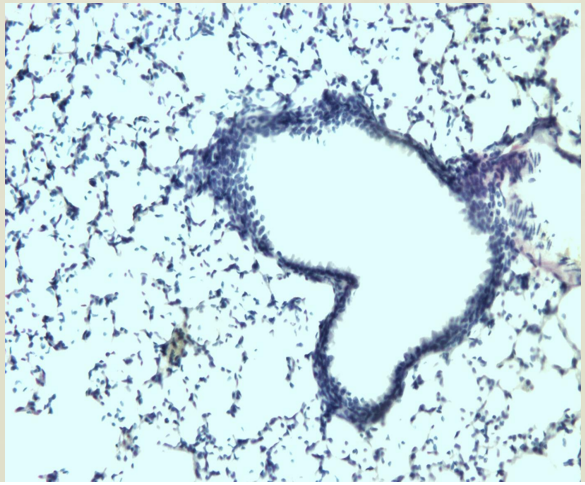
BeAl-T (1 week after exposure)



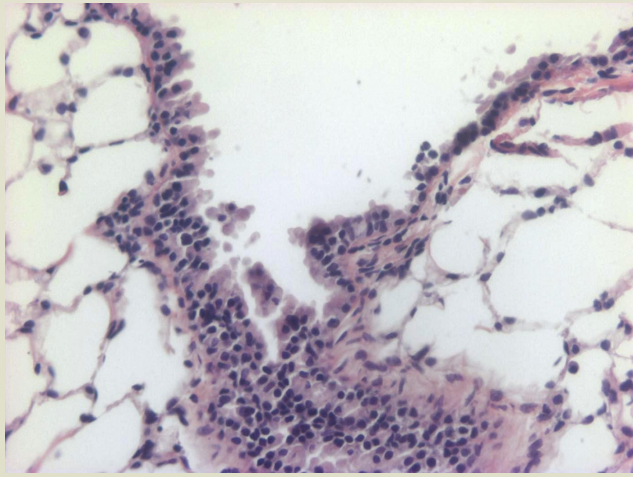
BeAl-F (1 week after exposure)



BeAl-T (3 weeks after exposure)



BeAl-F (3 weeks after exposure)



Histological score of lung inflammation 1 week after the end of exposure

1:no inflammation
2:mild inflammation
3:moderate inflammation
4:severe inflammation

	1	2	3
CTL	95,50%	4,50%	0
Be-F	0	54,50%	**45,50%**
Be-T	22,70%	68,20%	9,10%
BeO-F	22,70%	63,60%	13,60%
BeAl-F	44,40%	55,60%	0
BeAl-T	61,10%	38,90%	0

Histological score of lung inflammation 3 weeks after the end of exposure

1:no inflammation
2:mild inflammation
3:moderate inflammation
4:severe inflammation

	1	2	3
CTL	91,70%	8,30%	0
Be-F	0	29,40%	**70,6%**
BeO-F	0	75%	25%
BeAl-F	0	77,80%	22,20%
BeAl-T	0	100%	0

Conclusion

- What is the impact of particle size on Be toxicity ?
  - **Be tissue concentrations were significantly higher in mice exposed to Be-F and BeAl-F.**
  - **Significant difference of lung inflammation between fine and total particles for Be and BeAl.**
  - **Cytokine production was significantly higher in mice exposed to Be-F and BeAl-F.**

Conclusion

- What is the impact of chemical form on Be toxicity?

For total particles:

- Be in lung, spleen and liver were higher in mice exposed to Be compared to BeAl.
- Be concentrations were higher in blood in mice exposed to BeAl compared to Be.

Conclusion

- What is the impact of chemical form on Be toxicity?

For fine particles:

- Be concentrations in lung were higher in mice exposed to BeO compared to Be and BeAl.
- Be concentrations in blood were higher in mice exposed to BeAl compared to Be and BeO.

Conclusion

- What is the impact of chemical form on Be toxicity?

  - Lung inflammation was significantly higher in mice exposed to Be than BeO.

Conclusion

- This study is a unique murine model to investigate the importance of particle size in producing chronic lung disease.
- Our results are a first attempt at duplicating the immunologic findings that characterize workers exposed to Be compounds at the workplace.
- This model will provide information allowing identification of a scientifically based threshold to protect workers against CBD.

Acknowledgements

University of Montreal

Dr. Joseph Zayed, director
Lise Gareau, Elmirah Alyeva , Julienne Lama, Suzanne Philippe

McGill University

Dr. Bruce Mazer
Fariba Salehi
Severine Audessou

University of Quebec in Montreal

Dr. Gaston Chevalier

IRSST

Ginette Truchon
Yves Cloutier

This research was supported by the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST), QUEBEC, CANADA.